

When applying linear models to these steps, the researchers calculated that benzene is responsible for 8–48% of all smoking-induced leukemia deaths and 12–58% of smoking-induced AML deaths. These results, the researchers say, are reasonable, compared to published data on the numbers of such deaths. The quadratic model yielded far less plausible results, suggesting that less than 1% of smoking-induced leukemia deaths are benzene related. Some studies have found benzene to be most strongly associated with AML, but the chemical's link to other forms of the disease has not been ruled out.

The study not only provides information on the quantitative contribution of benzene to cancer deaths from cigarette smoking, it also helps demonstrate the validity of linear models in extrapolating to low doses of benzene. Benzene is an important industrial chemical used in making nylon, film developer, and solvents. Industrial workers are exposed to benzene concentrations that are 10–100 times greater than those encountered by smokers. For the past decade, the Occupational Safety and Health Administration and the U.S. Environmental Protection Agency have used linear models to set workplace benzene standards and evaluate environmental risks, respectively; both are reviewing that approach. The researchers point out that their results, being plausible predictions, contradict the theoretical argument that linear models may overestimate the low-dose risk from benzene. The results also show that if there is a threshold dose below which benzene does not cause leukemia, it is considerably lower than that received by smokers.

The researchers caution, however, that benzene is not the only leukemia-causing chemical in cigarette smoke. They note that 1,3-butadiene, styrene, *N*-nitrosodi-*n*-butylamine, urethane, and radioactive elements are also suspected of being leukemogenic. Benzene, however, appears to cause a substantial proportion of the leukemia deaths induced by smoking. —Harvey Black

## Getting On Our Nerves

### The Long-Term Effects of Chlorpyrifos

In the United States, termite treatments with chlorpyrifos, a widely used organophosphate pesticide, are currently applied about 20 million times per year to houses and lawns, and 82% of U.S. adults have detectable levels of the chlorpyrifos metabolite known as TCP in their urine. Like other organophosphates, chlorpyrifos exhibits moderate acute toxicity, with symptoms that include diarrhea and increased urination, perspiration, tearing of the eyes, and salivation. In addition, it readily inhibits the enzyme plasma cholinesterase at low doses and red-blood-cell cholinesterase at high doses. Results of a study by Kyle Steenland of the National Institute for Occupational Safety and Health and colleagues in this month's issue give some suggestion of delayed neurological effects from exposure to chlorpyrifos, particularly among subjects with a history of poisoning [*EHP* 108:293–300].

First marketed in 1965, chlorpyrifos came into rapidly increasing use after chlordane was banned for termite applications in 1988. Summarizing reports from poison control centers, the U.S. Environmental Protection Agency has concluded that chlorpyrifos is one of the leading causes of insecticide poisoning in the United States: 4,000–5,000 cases of accidental chlorpyrifos exposure were reported in 1993–1994. However, few epidemiological studies on chlorpyrifos neurotoxicity have been conducted.

Accordingly, the authors conducted a study of 191 termiticide applicators who had used chlorpyrifos for at least one year between 1987 and 1997 in a 12-county area of North Carolina. The applicators had worked with chlorpyrifos for an average of 2.4 years, with an average of 2.5 years spent working with other pesticides. Steenland



**The cancer culprit.** New research shows that benzene in cigarettes is responsible for a significant proportion of deaths from leukemia and acute myeloid leukemia.

and colleagues note that before 1988 some of these applicators had used chlordane, so that compound was included in their analysis.

The test protocol included conducting interviews and taking work histories, as well as administering neurological tests. Among the latter were a vibrotactile sensitivity test and an evaluation of arm/hand tremor, manual dexterity, vision, smell identification, and nerve conduction velocity. The scientists also performed clinical examinations, which involved urine samples and buccal (inner cheek) swabs, as well as a questionnaire to be completed with listings of any neurological symptoms. These included trouble remembering during the previous month, loss of muscle strength, numbness or tingling in toes, and lack of coordination or loss of balance.

The average urinary TCP level for 65 recently exposed applicators was 629.5 micrograms per liter, as compared with 4.5 micrograms per liter for the general U.S. population. Few significant differences between applicators and controls were found in arm/hand tremor, vision, smell, nerve conduction velocity, or visuomotor or neuro-behavioral skills. On the other hand, the exposed group did not perform as well as controls in the pegboard test (which involves putting as many pegs into slots in a board as possible within a fixed time period) and some postural sway tests. Exposed subjects also reported significantly more memory and emotional problems, fatigue, and loss of muscle strength. Although the authors did not find evidence of these symptoms during their evaluation, they note that their quantitative tests may not have been adequate to detect them.

In general, Steenland and colleagues found few exposure-related effects for most tests, including the clinical examination. However, the exposed subjects consistently reported more current psychological and physical symptoms than the nonexposed subjects. The differences in symptoms were more marked for former rather than current applicators, suggesting a long-term effect. However, these differences were generally not more apparent for those with longer exposure to chlorpyrifos. Future studies should consider the temporal sequence of exposure and any self-reported symptoms. Although the North Carolina study involved a large, well-defined target population, the authors suggest that it may not be representative of all exposed workers and that caution should be exercised in generalizing its results.

—Julian Josephson